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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	RIGL-036CIP	5176

83092 7590 07/26/2011

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
07/26/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/293,670	FISHER ET AL.
	Examiner	Art Unit
	TERESA WESSENDORF	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 37-44 are pending and under examination in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 37-44, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as reiterated below.

New Matter Rejection

Claim 37 is drawn to a method of screening, comprising: introducing a library of at least 10^3 vectors encoding different candidate agents into a population of mammalian cells grown in vitro; subjecting the population of cells to a physiological signal, wherein said physiological signal stimulates a phenotype in said cells in the absence of the candidate bioactive agents; sorting the individual cells in the population on the basis of at least three optical properties by

fluorescent activated cell sorting (FACS), identifying a cell having a phenotype that is altered relative to other cells in the population; and sequencing the nucleic acid encoding said candidate agent in said cell that has an altered phenotype, thereby identifying said candidate agent in said cell.(Please note that the rejections and/or responses below have been modified to address the present claim amendments and/or applicants' arguments).

Claim 37 in its entirety (as a unit) is not supported in the as-filed specification.

Applicants point support for claim 37 in general as found in the specification at page 3, line 36 to page 4, line 5 which discloses:

> In accordance with the objects outlined above, the present invention provides methods for screening bioactive agents for the ability to alter or modulate alterations in cellular phenotypes. The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by separating the cells on the basis of at least three, four or five cellular parameters. The candidate agents can be part of a molecular library comprising fusion nucleic acids encoding the candidate bioactive agents.

In reply, the above-cited section does not support claim 37 in its entirety (i.e., as a unit). It is not clear as to applicants' reference to the support for claim 37 **in general.** Cf. with the claims of the parent issued patent US 6,897,031('031 patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the present

claim is also not supported in the parent application now issued '031 patent.

Applicants cite disparate sections of the specification to provide support for individual method steps or components recited in the general support of claim 37, for example:

1. **Mammalian cells grown in vitro:**

Applicants rely at page 10, line 20 of the specification for mammalian cells; for 10^3 library at page 10, line 9 and page 10, lines 10-12 for "*in vitro*" mammalian growth.

The specification at page 10, lines 10-12 recites:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^6 being particularly preferred, and at least about 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when as outlined below. The cells may be any cell phase, either synchronously or not, including M, G1, S, and G2. In a preferred embodiment, cells that are replicating or proliferating are used; this may allow the use of retroviral vectors for the introduction of candidate bioactive agents. Alternatively, non-replicating cells may be used, and other vectors (such as adenovirus and lentivirus vectors) can be used. In addition, although not required, the cells are compatible with dyes and antibodies.

There is nothing in the above cited section that recites for mammalian cells grown *in vitro*. The at least 10^3 refers to a **library of cells** and not to a library of **10^3 vectors encoding different candidate agents.** Throughout the specification reference for 10^3 is made for cells. Not a single, express positive reference is made in the instant or parent application 09/062330 (now USP 6,897,031patent) that the vectors are 10^3 library and encoding 10^3 different candidate agents. [Please see Example 2 which recites a single vector encoding a single agent.]

2. **Physiological signal-** page 9, lines 36-37 and page 34, line 5 which states:

> In another example, the measurements of cell cycle regulation are determined wherein the condition or environment of the populations of cells differs from one another. For example, the cells may be evaluated in the presence or absence of physiological signals, for example hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents (i.e. chemotherapeutics, etc.), or other cells (i.e. cell-cell contacts). In another example, the measurements of cell cycle regulation are determined at different stages of the cell cycle process. In yet another example, the measurements of cell cycle regulation are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population.

In reply, the full text is cited above rather than the text quoted by applicants which had been taken out of context. As such step 2 of the claim recites "**subjecting** the population of cells to a physiological signal that stimulates a phenotype in cells of the same type in the absence of the candidate bioactive agents". The specification above recites **evaluating** the cells in the presence or absence of physiological signals and not of the candidate bioactive agents. Page 34, line 5 below of the specification presents the same concept.

> For example, the **cells may be evaluated in the presence or absence of physiological signals**, such as **exocytic** inducers (i.e., Ca**, ionomycin, etc.), hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, or other cells (i.e. cell-cell contacts). In another example, **the measurements of exocytosis** are determined at different stages of the exocytic process. In yet another example, the measurements of exocytosis are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population. (Emphasis added.)

3. At **least three optical properties** - page 4, line 3 which recites:

> The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by, separating the cells on the basis of at least three, four or five **cellular parameters.** (Emphasis added.)

In reply, reference is made to at least three cellular parameters but not to the claimed at least three optical properties as in claim 37.

The specific optical properties are alleged to find support at page 34, lines 30 and 37:

> In a preferred embodiment, changes in light scattering are assayed to determine alterations in exocytosis in a population of cells. When viewed in the FACS, cells have particular characteristics as measured by their forward and 90 degree (side) light scatter properties. These scatter properties represent the size, shape and granule content of the cells. Upon activation of the cells with a pro-exocytic stimulus, both the forward and side scatter properties of the cells changes considerably. These properties account for two parameters to be measured as readout for the exocytic event. These properties change in proportion to the extent of exocytosis of the cells and depend on the time course of the exocytic events as well. Alterations in the intensity of light scattering, or the cell-refractive index indicate alterations in exocytosis either in the same cell at different times..

In reply, this section provides support for only two optical properties i.e., forward and side and for exocytosis phenotype and not any other cell phenotypes, as in claim 37.

4. **Sequencing to identify - page 28, lines 10-12 recites:**

> In a preferred embodiment, the fusion partner is a rescue sequence. A rescue sequence is a sequence which may be used to purify or isolate either the candidate agent or the nucleic acid encoding it.

In reply, not only does this section present a different concept but also it relates to a compound, fusion partner. The claim is to a sequencing steps or procedures by which the presumably isolated and identified agent is sequenced. Because the specification, even the above quoted support, does not disclose a single candidate agent that has been isolated and identified hence, it is not seen how sequencing can occur.

Accordingly, claim 37 in its entirety or the disparate sections cited by applicants do not support the presently amended claims. Claims in its entirety should appear in the specification as in the claim to make clear what applicants are claiming and not picking and choosing disparate elements/ sections in the specification to make up a claim. Cf. with the claims of the parent issued patent US 6,897,031(‘031 Patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the claim is not supported in the parent application, now the issued ‘031 Patent.

Response to Arguments

Applicants argue that support for a claim need not be in one place in the specification. See e.g., MPEP § 2163.05. Since the Examiner has not cited any authority to support her assertion that support for a claim needs to be in one place in the specification (as a unit) and the Applicants cannot find any requirement for such, the Applicant submits the Examiner's comments in this section carry no weight.

In reply, the court in Net MoneyIN Inc. v. VeriSign Inc., No. 07-1565, slip op. at 17-18 (Fed. Cir. Oct. 20, 2008) states:

"Unless a single prior art reference describes "all of the limitations claimed" and "all of the limitations [are] **arranged or combined in the same way** as recited in the claim, it cannot be said to prove prior invention of the thing claimed….." A single prior art reference must "clearly and unequivocally" describe the claimed invention "without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." Id. at 19 (citing In re Arkley, 455 F.2d 586, 587 (C.C.P.A. 1972)). (Emphasis added.)

The above case law can appropriately apply to the instant claim which requires the art to correspond to the claim arranged in the manner as claimed (as disclosed in the specification.)

And, not picking and choosing unrelated (implicit) sections or teachings of the specification to make up the claim. The claim picking, choosing and combined from various parts of the disclosures which do not seem to directly relate to each other is not supported in the as-filed specification. The presently claim method is broader in scope than the original disclosure. The as-filed specification does not provide support for the picking and choosing of disparate elements of the specification and arrange in a manner as presently claimed.

Mammalian cells grown in vitro

Applicants argue that the method can be done using mammalian cells is explicitly described on page 10, line 20, of the instant application:

> Preferred cell types for use in the invention will vary with the cellular phenotype to be modulated. Suitable cells include, but are not limited to, **mammalian cells**, including animals {rodents, including mice, rats, hamsters and gerbils), primates, and human cells, particularly including tumor cells of all.

That the method can be done using cells grown in vitro is explicitly described at page 10, lines 10-14 of the instant specification:

> 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell types from

> either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when, as outlined below). The cells may be in any cell phase, either synchronously or not, including M

In reply, the above section(taken out of context from the full text below, page 10, lines 8-10) relates to a population of cell types from either a primary or secondary cultures, and not to a library of 10^3 vectors transfected into the cells grown in vitro.

Applicants argue that the method can be done using a library of at least 10^3 vectors is implicitly supported at page 10, lines 8-10:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^6 being particularly preferred, and at least about 10^8 to 109 being especially preferred. The population or sample can contain a mixture of different cell [types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when as outlined below). The cells may be in any cell phase, either synchronously or not, including M…]

in combination with page 21, lines 1-2, which states that in certain cases the target cells contain a single vector:

> In addition, it is possible to configure a retroviral vector to allow inducible expression of retroviral inserts after integration of a single vector in target cells: importantly, the entire system is contained within the single retrovirus. Tet-inducble retrovirus have been designed incorporating the self-..

Applicants alleged that if there are at least 10^3 cells each containing a single vector, then there is implicit support for 10^3 vectors. Applicants further note that the introduction of libraries of agents of various complexities into a population of cells is discussed on page 19 of the specification. Since there may be at least 10^3 cells, it follows that there may be 1^03 vectors.

In reply, the above section states integration of a single vector in target cells which is contrary to applicants' assumption of 10^3 cells implying 10^3 vectors. [Please see Example 2 which recites a single vector encoding a single agent.]

Page 9 does not relate to a 10^3 vector which states:

> Although it is difficult to gauge the required absolute size of an interaction library, nature provides a hint with the immune response…

Physiological signals

Applicants argue that evaluating cells in the presence or absence of a physiological signal implicitly requires that the

cells are subjected to a physiological signal. As such, "subjecting" a population of cells to a physiological signal is implicitly supported in the specification.

In reply, “evaluating” is not an implicit teaching of “subjecting”. Thus, the steps of subjecting and evaluating would be broader in scope than the originally filed evaluating step. See MPEP 2163[R5] B.

At least three optical properties

Applicants argue that the cellular parameters by which a cell is sorted are in fact optical properties. See, e.g., the entire application particularly the context given on page 34, lines 30-37, which states that the characteristics of a cell can be measured by light scatter properties. Moreover, in the flow cytometry arts (and consistent with how the term is used in the instant application) a "parameter" corresponds to an optical property (e.g., fluorescence, side scattering, etc).

In reply, as correctly stated by applicants, page 34, lines 30-37 recite only light scatter properties. The claims recite that the optical properties are sorted by FACS and not that the FACS parameters are applied to sort the claim three optical properties. The argued various parameters are not commensurate

in scope with the claim 3 optical properties. The test whether or not the amendment constitutes new matter is whether or not the claim limitations would indicate to one skilled in the art that the inserted step(s) formed part of applicants' original disclosure (invention), not that it is known in the art.

Sequencing to identify

Applicants state that Supplemental support for this element (in addition to the last cited passage on page 28, lines 10-12) is found on page 32, lines 34-36 as shown below.

> In a preferred embodiment, the bioactive agent is characterized. This will proceed as will be appreciated by those in the art, and generally includes an analysis of the structure, identity, binding affinity and function of the agent. Generally, once identified, the bioactive agent is resynthesized and...

Applicants submit that because the structure of a nucleic acid is defined by its nucleotide sequence, the "analysis of the structure" of a nucleic acid provides **implicit** support for sequencing the nucleic acid. (Emphasis ours).

In reply, in addition to the response in the last office action, the above section does not recite the claim sequencing step, which is a species not included in the various characterization of the agent. Analysis of the structure is not

necessarily sequencing of the structure. The structure can be analyzed in terms of the atoms present or arrange in the molecule or other chemical or physicochemical analysis of the structure.

Written description Rejection

Claims 37-44, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as reiterated below.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the genus of the invention.

Applicants are not in possession of the claim method in general as recited in claim 37. The specification at the time of filing does not describe a library of 10^3 vector encoding presumably also 10^3 different kinds of candidate agents. It does not describe all or any kinds of vectors, whether of the

same or different type that would encode any or all kinds of different agents. There is no description of a candidate agent that has been isolated or identified by the encoded diverse library of 10^3 vectors that alters a phenotypic change to any population of mammalian cells. Throughout the specification reference is made only to a library of population of 10^3 but not to a 10^3 library vector that encodes (absent any gene or nucleic acid therein) an enormous numbers of different kinds of candidate agents. The specification' working example describes the effect of a single candidate known agent p21 and its phenotypic effect to a population of 10^3 cells. There is no description of how the single known p21 has been selected, purified and identified from the 10^3 library of vectors, itself encoding said agents. Nor is there a description of the candidate agents that alters any or all kinds of phenotypes in a population of cell. Since no identification of a candidate peptide agent has been made and the single protein (not peptide) is known hence, it is not readily apparent how sequencing can be done to an already known protein. There are no characterizing features of the genus candidate agent coupled with a functional limitation or core sequences corresponding with the single protein described in the specification to lead a skilled artisan to the general method.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

Response to Arguments

Applicants argue that libraries of vectors are generically described in the instant specification at, e.g., page 19, line 31 to page 21, line 11. Moreover, libraries of vectors are conventional in the art (see, e.g., Nolan / WO 97/27212), which is cited by the Examiner in an obviousness rejection that is discussed below. Thousands of other publications describe the production and use of libraries of vectors. Since the guidelines clearly state that "the description need only describe in detail that which is new or not conventional" and "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail", there is no need for the Applicants to

provide a detailed description of libraries of vectors that can be used in the rejected claims. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work.

In reply, the general term "library of vectors" might be known in the art as argued. However, as applied in the context of the claim method (which applicants alleged is novel) the library of vectors together with the undefined components of the process steps are not adequately described in the (original) disclosure. As stated above, the original disclosure describes only the single known p21 protein, the selection, encoding the candidate agents as claimed are not clearly apparent. Furthermore, even assuming, for the sake of arguments, that the single p21, a known protein, suffice as written description for the huge scope of the claim (which it does not), the disclosure does not indicate such. There is no correlation made in the specification that this single protein is of common structure or function to the huge scope of the claim active agent of the method.

Thus, the claim method standing alone or together with the huge components use in the process is not adequately described at the time applicants' invention was made.

The Federal Circuit has cautioned against over reliance on the assertion that everything needed to practice the full scope of the claims was "known in the art" and that a patent need not teach, and preferably omits, what is well known in the art. See Genentech Inc. v. NovoNordiskA/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997): "[T]hat general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement (written description).... It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement." Here, the specification does not teach the method steps (alleged to be novel) and the components use in the method such as the broad 10^3 vectors encoding candidates agents transfected into any mammalian cells in vitro to identify and sequence the candidate agent. Applicants point to nothing in the specification that would indicate to the contrary.

Enablement Rejection

The enabling disclosure provided in the specification is not commensurate in scope with the recited general method. The method employs broadly a huge 10^3 library vectors itself encoding directly any of the different candidate agent that affects any phenotype type of any cell in a population. The specification provides only broad generalized statements. It would take an undue amount of experimentation to determine the 10^3 library of vectors encoding different candidate agents that alters any type of phenotype to any kind of cells in a population. This is made more complex since the specification does not provide support for the claim general method. (Please see the new matter rejection above.)

The factors that are to be considered in the determination of undue experimentation are disclosed in In re Wands, (U.S.P.Q. •2d 1400 (CAFC 1988). These include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, and the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to make the 10^3 library of vectors encoding any candidate agent(s). The specification describes only a 10^3

library of cell population. Therefore, the specification does not teach how to go about making a vectors of 10^3 library of different kinds encoding different kinds of candidate agents. The specification does not describe from the 10^3 library the candidate agent that has phenotypically alter a population of cells to enable its isolation, identification and sequencing.

2). Applicants have failed to provide any working examples for a 10^3 library of any kind of vectors, whether the same or of different type encoding an enormous diverse kinds of candidate agents that alter a number of phenotypes of a cell population. The working example provides for a single, known protein p21. It is not apparent from the specification whether this single, known protein is the one obtained from the encoding library of vectors, isolated from the rest of the cells, identified and sequenced. The specification does not teach the sequence of the p21, and if it is known, the need for its sequencing.

3). The state of the prior art is such that the consequences of some bioactive agent and cell interaction on some cells have not yet been fully determined or elucidated. See Polyak (Genes and Development) at e.g., page 1945, col. 2. 4).

The art is inherently unpredictable with respect to the numerous types of agents altering even a single phenotype of a single cell let alone a population of cells. Also, the use of a wide variety of libraries with candidate agent presentations can be displayed in an extraordinarily large number of conformations. See Luo (Nature) e.g., at page 159, col. 2, first incomplete paragraph. Nakanishi (The EMBO Journal) e.g., at page 556, col. 2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2. 5). The breadth of the claims encompasses large possible combinations for the different unnamed or undefined variables of library of vectors, candidate agents, phenotypes and cell population.

6). While the level of skill in the art is high, the molecular biology and gene art is so unpredictable that it would require undue experimentation to make the invention commensurate in scope with that claimed in the absence of adequate guidance or direction as set forth above. This is especially true when the present claim is described in general and not supported in particular by the specification. The specification provides only definitions of the terms use in the general method. For example, at page 16, line 8 up to-page 30, line 15 the term "candidate bioactive agent" is defined as any molecule, e.g., protein,

small organic molecule, carbohydrates (including polysaccharides), polynucleotide, lipids, etc.

Applicants' disclosure would not enable a skilled artisan to carry out the claimed methods without undue experimentation. The specification does not provide support for the generic method and only provides definitions for the broad components in the method.

Response to Arguments

Applicants state that the Examiner is requested to apply the arguments in the prior section of this response to this rejection. Specifically, the Applicants submit that libraries of vectors are conventional in the art and, as such, their making and use does not require undue experimentation. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work.

In reply, the arguments above are applied herein as requested. Furthermore, the making and using of the libraries is but one aspect of the invention. It is the claimed invention as a whole that would require undue experimentation. The disclosure

provides only general statements and the argued implicit teachings in the specification. The single working example teaches the known protein (p21) which is not taught to be obtained from the alleged novel process.

As applicants submit above the structure of a nucleic acid is defined by its nucleotide sequence hence the claimed sequencing, as applicants argued above, implies that the bioactive agent has been identified by its structure.

The specification does not enable the alleged novel method in its entirety. There is not a single working example that shows that the claim method works specifically employing broad components in the method. It would take undue amount of experimentation to practice the claim method lacking any guidance/direction as to how a skilled in the art would proceed.

Withdrawn Rejections

In view of the amendments to the claims and applicants' arguments, the 35 USC 112, 2nd paragraph rejection in the last Office action is withdrawn.

Claim Rejections - 35 USC § 112, 2nd paragraph-Necessitated by Amendments

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is vague and indefinite as to whether the new limitation "cells" are the same or different from the mammalian cells that serve as physiological signal. There are no distinguishing features of the "cells" to differentiate it from the mammalian cells, especially with the cancellation of the term "other".

Claims 37, 40 and 42-43 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification does not provide support for the new claim limitation of the broad claim “cells” in claim 38 or the two steps as recited in claim 37, second step. MPEP 2163.06 clearly states that applicants point out where in the as-filed specification, the new claim limitations find support.

Claim Rejections - 35 USC § 103

Claims 37, 40 and 42-43, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Uhr et al (USP 5612185) for reasons of record as reiterated below.

For claims 37, 40 and 42-43; Uhr discloses at e.g., col. 3, line 50 up to col. 4,line 37; a method of identifying a candidate substance, capable of inducing alteration of cellular phenotype comprising contacting the population of cells to be analyzed with a panel of (library of candidate agents) directed against distinct cell surface molecules, under conditions effective to allow antibody binding. The antibodies would be labelled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths (reads on the claim at least 3 optical parameters), it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal (reads on claim 40). Thus cells can be separated on the basis of 6 parameters (reads on claim 37). The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using **fluorescence-activated flow cytometry**. Uhr discloses that

for multiparameter cell sorting, it is contemplated that one would wish to employ a combination of agents that results in independent signals of 4 different wavelengths. This may be readily achieved by using four distinct monoclonal antibodies. Alternatively, the fourth signal may be supplied by employing a DNA stain which results in color generation, such as Hoechst, and in these circumstances only three monoclonal antibodies may be used in the separation procedure. Uhr further discloses at e.g., cols. 7-14, Table 1 the panel of antibodies. Uhr discloses or suggests at e.g., col. 22, lines 14-20 the preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes introduced into the cells to be treated. The replication defective retrovirus (reads on claim 43) may be used, as may other vectors. **Fig. 1 discloses that Flow cytometry was performed on a FACS wherein forward light scattering, orthogonal light scattering, FITC and PE signals were determined for 30,000(3 x10^4) cells.** FIG. 3 shows cDNA synthesized from a mixture of 10^4 cell-equivalents of total RNA and 10^6 (myc and fos panels) or 10^7 (actin panel). BCL1 cells bear surface immunoglobulin of both the mu/lambda and delta/lambda isotypes that share a common idiotype (Id), as defined serologically and by sequence analysis (Krolick et al., 1979).

Uhr further discloses at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.** (Emphasis added).

Uhr, alone, discloses or teaches all the elements of the claim method except the sequencing of the candidate agents. Such sequencing would have been obvious to one having ordinary skill in the art at the time the invention was made given the known structure of antibodies or antigens taught by Uhr.

Response to Arguments

Applicants argue that Uhr's disclosure is deficient for a number of reasons. For example: a) Uhr does not teach the use of a library of at least 10^3 vectors encoding different candidate agents, as required by the rejected claims. Uhr describes the use of a vector that encodes c-jun or c-fos into cells to induce cell cycle arrest. Thus, at best, Uhr suggests a method that employs one of two vectors (which encode c-jun or c-fos). Based on Uhr's disclosure, there would be no reason to use more than two different vectors, let alone at least 1,000 vectors as

required by the rejected claims. Uhr's Fig. 3 provides no evidence that Uhr discloses "a library of at least 10^3 vectors encoding different candidate agents" much less introducing such a library into a population of mammalian cells grown in vitro.

In reply, as stated by applicants above, under the new matter issue; "if there are at least 10^3 cells each containing a single vector, then there is implicit support for 10^3 vectors. Following applicants' logic, Uhr teaches at Fig. 1 Flow cytometry performed on a FACS wherein forward light scattering, orthogonal light scattering, FITC and PE signals were determined for **30,000(3 x10^4) cells.** FIG. 3 shows cDNA synthesized from a mixture of **10^4 cell-equivalents of total RNA and 10^6 (**myc **and** fos panels**)**.

Applicants further argue that the introduction of libraries of agents of various complexities into a population of cells is discussed on page 19 of the specification. Since there may be at least 10^3 cells, it follows that there may be 10^3 vectors.

In reply, as admitted in the specification at page 19, the size of the library is known in the art, nature provides a hint with the immune response diversity of 10^7-10^8. Published in vitro selection techniques have also shown that a library size

of 10^7 to 10^8 is sufficient to find structures with affinity for the target.

b) Uhr does not introduce candidate agents into cells and subject the cells to a physiological signal as separate events, as required by the rejected claims. Uhr merely introduces compounds (c-jun or c-fos) into cells to induce cell cycle arrest. At best, the compounds can either be considered candidate agents (in which case there is no separate physiological stimulus) or as physiological stimuli (in which case there is no candidate agent). Either way, introducing candidate agents into cells and subjecting the cells to a physiological signal as separate events is not disclosed by Uhr. Applicants argue that they have been amended to make it clear that the introducing of the candidate agents into cells and subjecting the cells to a physiological signal are done as separate events.

In reply, as stated above the steps of “subjecting” is not supported in the as-filed specification. Again following applicants arguments or logic that "subjecting" is implicit of “evaluating” hence, Uhr which teaches the evaluating would

indicate that the cells have been subjected to physiological signal.

Physiological signal is defined in claim 38 as an exocytic inducer, a hormone, an antibody, a peptide, an antigen, a cytokine, a growth factor, an action potential or cells.

Uhr teaches at e.g., col. 15, line 27+:

> The compositions for use in inducing tumor cell cycle arrest may further comprise pharmaceutical agents (physiological signal) other than antibodies or agonists(bioactive agent, as claimed) that are capable of inducing or maintaining cell cycle arrest (cell phenotype, as claimed). Such components are contemplated to include, for example, cytokines…such as gamma IFN and TGF .beta.; compounds which induce terminal differentiation, including polar/apolar compounds such as hexamethylene bisacetamide, and also retinoic acid; and agents which interfere with signal-transduction in a specific tissue.

When read in light of the disclosure teachings, Uhr similarly measures or evaluates cell-cell or antigen-antibody interaction, inter alia, that is included in the broad scope of the claim physiological signal.

c) Applicants argue that Uhr does not disclose using FACS to examine the individual cells in the cell population that has been grown in vitro. But recognize that the only FACS methods described in Uhr's disclosure are those in which the cells of spleens of animals are examined. Such cells are grown in vivo

rather than in vitro and, as such, this element of the claims is not provided. Applicants argue that in vitro cells described in this passage in Example 4 are not analyzed by FACS as taught in Fig.1.

In reply, Example 4 of Uhr teaches the advantage of in vitro over in vivo and teaches in Fig. 1 the FACS sorting of cells in vitro. Thus, since Uhr teaches the advantages of in vitro sorting hence this would be within the skill in the art to do motivated by said advantages of in vitro over in vivo.

d) Uhr does not disclose sequencing the nucleic acid encoding the candidate agent in a cell that has an altered phenotype. Since the identities of Uhr's clones (which, at best would encode c-jun or c-fos) would be known before any experiments were initiated, there would be no need for this step to be performed. Applicants have provided alternative support for the sequencing step of the claimed method.

In reply, attention is drawn to Uhr which teaches at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The**

> **preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.** (Emphasis added).

Furthermore, Uhr discloses at e.g., Fig. 3:

> BCL1 cells bear surface immunoglobulin of both the mu/lambda and delta/lambda isotypes that share a common idiotype (Id), as defined serologically and by **sequence analysis** (Krolick et al., 1979). (Emphasis added.)

Read in light of the specification, the disclosure does not define any sequencing step or any candidate agent that has been identified such that sequencing is done.

The Examples in the specification, like Uhr, also uses known candidate agents and does not teach an isolated and identified candidate agent that has been sequenced.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhr in view of Hide.

Uhr is discussed above. Uhr discloses a FACS means of measuring the altered cellular phenotype but not exocytosis induced by Ca++ or ionomycin.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of

the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Hide further disclose at e.g., page 592 that a suboptimal concentration of the stimulus ionomycin will distinguish between populations of cells that have differing thresholds to stimulus by intracellular Ca++. The strength of the stimulus selects the cells which then proceed to a full degranulation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Uhr by exocytosis using such stimulus as Ca++ or ionomycin as taught by Hide. Hide teaches that exocytosis measurement when stimulated by Ca++ or ionomycin will distinguish between populations of cells that have differing thresholds. The strength of the stimulus would select the cells which then process to full exocytosis. One would have been motivated to use stimulus as Ca++ or ionomycin to differentiate one cell from another by the effect of the stimulus. One would have a reasonable expectation of success since exocytosis phenotype has been used to differentiate cells in a population using FACS as successfully shown by the works of Hide.

Response to Arguments

Applicants recognize that Hide is cited solely to provide a FACS-based method for assaying a population of cells that have been stimulated by Ca++ or ionomycin. But argue that none of Uhr's deficiencies discussed above is met by Hide's disclosure and, as such, taken in any combination, Uhr and Hide fail to teach or suggest all of the elements of the rejected claims.

In reply, Hide is employed as applicants recognize for its teachings of exocytic signal. This is the only element not taught by Uhr. Accordingly, the combined teachings of Hide and Uhr would lead one having ordinary skill in the art to the claim method as Hide provides the motivation for the use of exocytic stimulus.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhr in view of Conneally for reasons of record as reiterated below.

Uhr is discussed above. Uhr does not positively teach library of retroviral vectors albeit, at least suggests said library of retroviral vectors. However, Conneally positively teaches at e.g., page 461, under the Discussion heading, the

advantages in the use of recombinant retroviuses for the genetic modification of cells. One of the advantages is the ability to assess gene transfer to specific subpopulations of cells immediately after infection. The detectable level is sorted by FACS. The use of recombinant retroviral vectors to transfect cells would have been obvious to one having ordinary skill in the art at the time the invention was made as taught by Conneally and at least contemplated by Uhr. The advantages provided by Conneally above would provide the motivation to use this recombinant virus. One having ordinary skill in the art would have a reasonable expectation of success in using retroviral vectors. These vectors have been conventionally use in the art and has been successfully employ in the art as taught by Conneally and at least suggested by Uhr, especially in transfecting mammalian cells.

Response to Arguments

Applicants argue that none of Uhr's deficiencies discussed above is met by Conneally's suggestion to use retroviral vectors and, as such, taken in any combination, Uhr and Conneally fails to teach or suggest all of the elements of the rejected claims.

In reply, Uhr already suggests retroviral vectors. Conneally is employed to show that retroviral vectors are

conventionally employed in the art of vector use and the motivation of retroviral use.

2. Claims 37 and 40-44, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Nolan in view of Jia-ping and Uhr et al for reasons of record as reiterated below and Board's decision mailed on 7/21/10.

Nolan et al discloses at e.g., page 31, line 1 up to page 32, line 6 a method comprising introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The plurality of cells is then screened for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent. Any phenotypic change may be observed, detected, or measured on the basis of the screening methods. Suitable phenotypic changes include, but are not limited to gross physical changes such as changes in cell morphology, cell growth (cell cycle, as claim), cell viability (apoptosis, as claim), changes in the expression of one or more RNAs, proteins, changes in the localization of one or more RNAs, proteins, changes in the bioactivity or specific activity of one or more RNAs, proteins, changes in the secretion of ions,

cytokines, hormones, growth factors, or other molecules and etc. (reads on the claim physiological signal). The altered phenotype is detected in a wide variety of ways and will generally depend and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example, Standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds after killing the cells. Once a cell with an altered phenotype is detected, the cell is isolated from the plurality which does not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, FACS or other cell vitality indicator dyes.

Nolan does not disclose a method in which the cellular phenotype is exocytosis and at least 3 optical parameter cell sorting by FACS (although suggests said FACS analysis). However, Jia-ping discloses a method of sorting cells by multi-parameter

sorting technique using flow cytometer including exocytosis. The method provides for an increase of purity of the divided cell and further information of the different cell subpopulations (page I).

Uhr is discussed above. It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the changes in the exocytosis phenotype of a cell by at least 3 optical parameters in the method of Nolan in the manner as taught by Jia-ping and Uhr. One having ordinary skill in the art would have been motivated to sort the alteration in the phenotypic cells by at least 3 parameters based on exocytosis phenotype of the cell for the advantages taught by Jia-ping and Uhr. The alteration in the exocytosis phenotype of the cell provides further information of the different cell subpopulations such that an increased purity of the divided cell is obtained.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr et al as applied to claims 37 and 40-44 above, and further in view of Hide et al.

Nolan is discussed above. Nolan discloses a FACS means of measuring the altered cellular phenotype but not exocytosis induced by Ca++ or ionomycin.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Hide further discloses at e.g., page 592 that a suboptimal concentration of the stimulus ionomycin will distinguish between populations of cells that have differing thresholds to stimulus intracellular Ca++. The strength of the stimulus selects the cells which then proceed to a full degranulation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis using such stimulus as Ca++ or ionomycin as taught by Hide. Hide teaches that exocytosis measurement when stimulated by Ca or ionomycin will distinguish between populations of cells that have differing thresholds. The strength of the stimulus would select the cells which then process to full exocytosis.

One would have been motivated to use stimulus as Ca++ or ionomycin to differentiate one cell from another by the effect of the stimulus. One would have a reasonable expectation of success since exocytosis phenotype has been used to differentiate cells in a population using FACS.

Response to Arguments

Applicants argue that the claims are submitted to be fully supported in the instant application and in parent application serial no. 09/062,330, now issued as U.S. patent 6,897,031.

In reply, the Board's decision at pages 12 -14 states:

The filing date of the instant application is April 16, 1999 (see Transmittal of New Application (entered April 16, 1999)), which is more than one year after the publication date of the Nolan reference.

The Specification states that "[t]his application is a continuation-in-part of U.S. Application Serial No. 09/062,330, filed on April 17, 1998 [now U.S. Patent No. 6,897,031 B1], and U.S. Application Serial No. 09/157,748, filed on September 21, 1998 (Specification 1 (as amended September 24, 2004)).

Thus, to remove the statutory bar set by 35 U.S.C. § 102(b) against patenting claims anticipated or obviated by printed

publications available more than one year prior to an application's filing date, Appellants' claimed subject matter must find support in Application Serial No. 09/062,330(‘330 application), filed on April 17, 1998, which issued as U.S. Patent No. 6,897,031 B1.

The Examiner finds: The 09/062330 (now US Patent 6,897,031) ('031 Patent) does not provide support for now newly presented claim 37 in its entirety (cf. with the ‘330 application) and remainder of the claims as given in the new matter rejection above. **For example**, the new claim to a “library of at least 10^3 vectors encoding different candidate agents”; “subjecting” the population of cells to a physiological signal that stimulates a phenotype in cells in the absence of the candidate bioactive agents”; "at least 3 optical properties" as applied to the different claim cellular phenotypes and “sequencing of the nucleic acid encoding said candidate agent”.

The '031 patent teaches:

> …[A] method for screening for alterations in **exocytosis of a population of cells** (not the now presently broad claimed physiological signal) The cells are sorted by a FACS machine by assaying for alterations in at least three of the properties(not optical properties, as broadly claimed for the broad physiological signal) selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule

> binding, surface granule enzyme activity, and the quantity of granule specific proteins. Methods for screening for bioactive agents capable of modulating **exocytosis** in a cell are also described…. (not sequencing)('031 patent, e.g., abstract). (Emphasis and parenthetical statements provided).

Applicants have not shown that the Nolan reference is unavailable as prior art against the presently rejected new claims. To avoid the statutory bar set by 35 U.S.C. § 102(b), Appellants must find descriptive support for the rejected claims in a priority application filed less than one year after publication of the Nolan reference. In the instant case, only the '330 application, which issued as the '031 patent, and which is asserted as a continuation-in-part parent to this application, has such a filing date (see FF 15).

Applicants are also directed to the further responses of February 24, 2006, as relied upon by applicants above.

Thus, the presently claimed broad method is not supported in the '031 patent, which is a CIP thereof.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is

reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1636